REMARKS

Claims 1, 3-35, 37-43, 50-55 and 61-74 were pending in the subject application. By this amendment, applicants have canceled claims 55 and 67-74. Accordingly, claims 1, 3-35, 37-43, 50-54 and 61-66 are pending in the subject application.

In section 2 of the March 24, 2004 final Office Action, the Examiner stated that, in view of applicants' November 3, 2003 response to the July 31, 2003 Office Action, the only grounds of rejection maintained are the obviousness-type double patenting rejections of claims 1, 3-35, 37-43, 50-54 and 61-66.

Applicants are pleased to learn that the obviousness rejections under 35 U.S.C. § 103 have been withdrawn. Applicants note that the analysis required to establish obviousness under 35 U.S.C. § 103 is analogous to the analysis required to establish obviousness-type double patenting, as set forth in MPEP § 804 which provides:

> A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

> Since the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection, the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are employed when making an obvious-type double patenting analysis.

Because the Examiner has withdrawn the obviousness rejections under 35 U.S.C. § 103 of claims 1, 3-35, 37-43, 50-54 and 61-66 over the same set of references which are relied upon to support the obviousness-type double patenting rejections, applicants contend that the obviousness-type double patenting rejections should have also, logically, been withdrawn as to these same claims. Nevertheless, applicants proceed below to clarify the reasons for withdrawing the Examiner's rejections.

Double Patenting Over the '791 Patent in View of the '981 Patent

In section 3 of the March 24, 2004 final Office Action, the Examiner maintained the rejection of claims 1,3-35, 37-43, 50-54 and 62, 63 and 65 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 7-14 of U.S. Patent No. 6,214,791 to Arnon, et al., ("the '791 patent") in view of U.S. Patent No. 6,024,981 to Khankari, et al., ("the '981 patent"), for the reasons of record in the July 31, 2003 Office Action.

In the March 24, 2004 final Office Action, in response to applicants' remarks filed November 3, 2003 pointing out that

none of the cited references specifically teach or suggest the combination of glatiramer acetate (copolymer-1) as an active ingredient with microcrystalline cellulose (MCC) as a carrier, and that none of the references teach or suggest the use of at least 50% MCC in the formulation of a medicament, the Examiner repeated the allegation that MCC is well known in the art. In response to applicants' assertion that the '981 patent teaches away from the use of such high proportions of MCC in a medicament, the Examiner alleged that the '981 patent does teach that a typical range for a disintegrant such as microcrystalline cellulose is conventionally as high as 20% but can be increased for rapidly disintegrating dosage forms (column 13, lines 60-67 in particular). The Examiner also alleged that the fact that there are no specific examples with such a high proportion of MCC does not negate the Examiner's allegation that high percentages of MCC are taught by the '981 patent when rapid disintegration is desired. The Examiner further alleged that applicants' use of greater than 50% MCC in the formulation of a medicament comprising glatiramer acetate represents optimization of a formulation for enhanced dissolution properties and this is a skill that is well within the purview of a person having ordinary skill in the art at the time the invention was made and does not require particular inventive input. The Examiner alleged that contrary to applicants' assertion that the '981 patent teaches away from 50% MCC in the medicament, based upon the cited teachings of the '981 patent the artisan would have a reasonable expectation of success in improving the rapid dissolution of the medicament by the use of percentages of MCC higher than 20% and a reasonable expectation of success is all that is required by the statute, citing *In re* Vaeck, 20 USPQ 1438 (Fed. Cir. 1991).

In response, applicants point out that claim 1 recites "an amount of microcrystalline cellulose in excess of 50 % by weight of the composition" and that none of the Examiner's cited references teach or suggest, implicitly or explicitly, making a pharmaceutical composition which comprises "in excess of 50 %" microcrystalline cellulose by weight.

Initially, applicants respectfully submit that the Examiner has misconstrued the language of the '981 patent. Specifically, the Examiner supports the instant rejection by relying on the paragraph which begins on column 13, line 60 and ends on column 14, line 2 of the '981 patent. This paragraph fails to support the Examiner's position and, in fact, supports the applicants'.

The first sentence of the above mentioned paragraph states, "[t]he conventional range of non-effervescent disintegrant agents used in conventional tablets can be as high as 20%."(emphasis added). Clearly, this defines an upper limit for the use disintegrant agents in general, of which microcrystalline cellulose is an example.

The second sentence states, "[h]owever, generally, the amount of disintegration agent used ranges from between about 2 and about 5%, according to the Handbook of Pharmaceutical Excipients." (emphasis added). This sentence clearly provides the typical range of microcrystalline cellulose that was used in the art.

The third sentence then teachs that, "[u]nderstandably, however, when a rapidly disintegrating dosage form is envisioned, the relative proportion of disintegration agent used will be increased." This third sentence must be taken in

the context of the first sentence, which provides an upper limit of 20% for the use of microcrystalline cellulose, and the second sentence, which provides the typical range of 2-5%. That is, the '981 patent teaches to one skilled in the relevant art that 2-5% would be the normal usage of microcrystalline cellulose but if rapid disinitegration is desired, one could increase the percentage of microcrystalline cellulose, perhaps to as high as 20%. The rationale for a different interpretation of this paragraph has not been set forth.

The fourth sentence reinforces this upper limit by stating "Cousins et al., for example, requires from about 6.1 to about 13.3% reticulated PVP, as described in its various examples." By providing examples of compositions with amounts of disintegrant in the range of about 6.1% to about 13.3%, i.e. less than 20%, the upper limit defined in the first sentence is reinforced. In fact, no amount above 20% of any disinitegrant is taught in the '981 patent.

Accordingly, one skilled in the relevant art would find no suggestion or motivation in the '981 patent to prepare a composition with greater than 20% of any disintegrant, let alone a composition with an amount of microcrystalline cellulose in excess of 50% by weight of the composition.

The use of in excess of 50 % microcrystalline cellulose by weight results in pharmaceutical compositions with excellent flow and mixing characteristics, improved dissolution and improved stability over that which would have been expected based on the properties of glatiramer acetate (see page 37, lines 17-32 of the subject application). Furthermore, based on the properties of glatiramer acetate, it was unexpected that

the formulation with microcrystalline cellulose, particularly in excess of 50 %, would have any, much less significantly, improved pharmaceutical properties suitable for oral administration (see page 38, lines 1-13 of the subject application). For example, the claimed formulation has an advantageous property in that it allows for matching *in vitro* dissolution profiles of the tablet that contains 5 mg of glatiramer acetate and the tablet that contains 50 mg glatiramer acetate tablets weight as shown in Figure 3. Specifically, and unexpectedly, even though the tablet containing 50 mg of glatiramer acetate is four times the weight of the tablet containing 5 mg of glatiramer acetate (see page 24, Table 5), the tablets have similar dissolution profiles. (see page 37, line 29 to page 38, line 13). It is unexpected based on the prior art that the use of in excess of 50 % by weight microcrystalline cellulose will produce such advantageous properties in the pharmaceutical compositions of the subject invention.

Clearly the '981 patent provides no support for the rejection of claims reciting microcrystalline cellulose in excess of 50%. Therefore, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1,3-35, 37-43, 50-54 and 62, 63 and 65 based on obvious-type double patenting over the '791 patent in view of the '981 patent.

Double Patenting Over the '791 Patent in View of the '981 Patent and the '600 Patent

In section 4 of the March 24, 2004 final Office Action, the Examiner maintained the rejection of claims 1, 20, 21, 22, 43 and 64 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 7-

14 of the '791 patent in view of the '981 patent and U.S. Patent No. 5,965,600 to Sato, et al., (the '600 patent), for the reasons of record in the July 31, 2003 Office Action.

In the March 24, 2004 final Office Action, the Examiner noted applicants' argument that the citation of the '600 patent does not render the combination of glatiramer acetate (copolymer-1), greater than 50% MCC and an enteric coating obvious. The Examiner's comments regarding the combination of the disclosures of the '791 patent and the '981 patent have been discussed, *supra*, in section 3. The Examiner also alleged that the use of an enteric coating on the claimed medicament would have been obvious to the artisan because the use of both enteric and film coatings is "customary" in the art and in the present instance would be particularly so because, as a proteinaceous active ingredient, glatiramer acetate would be particularly subject to acidic degradation in the stomach, which may reduce it's effectiveness in the treatment of MS.

In response, the applicants reiterate their remarks above and maintain the combination of the '791 and '981 patents with the '600 patent does not make obvious to one skilled in the art a tablet containing the combination of glatiramer acetate, an amount of microcrystalline cellulose in excess of 50% by weight of the composition, a film coating and an enteric coating. As discussed above, neither the '791 patent nor the '981 patent alone or in combination, suggest, teach or motivate the use of an amount of microcrystalline cellulose in excess of 50% by weight of the composition. Furthermore, as acknowledged by the Examiner, the '791 patent and the '981 patent do not disclose the use of either a film coating or an enteric coating. The '600 patent does not disclose the use of an amount of microcrystalline cellulose in excess of 50% by

weight of the composition. Therefore, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 20, 21, 22, 43 and 64 based on obvious-type double patenting over the '791 patent in view of the '981 and '600 patents.

Double Patenting Over the '791 Patent in View of the '981 Patent and the '800 Patent

In section 5 of the March 24, 2004 final Office Action, the Examiner maintained the rejection of claims 1 and 61 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 12-14 of the '791 patent in view of the '981 patent and U.S. Patent No. 6,162,800 to Dolle, et al. ("the '800 patent"), for the reasons of record in the July 31, 2003 Office Action.

In the March 24, 2004 final Office Action, the Examiner noted that applicants argued that the additional citation of the '800 patent does not render the combination of glatiramer acetate (copolymer-1), greater than 50% MCC and a protease inhibitor obvious. The Examiner's comments regarding the combination of the disclosures of the '791 patent and the '981 patent have been discussed, *supra*, in section 3. The Examiner also alleged that the use of a protease inhibitor as part of the claimed medicament would have been obvious to the artisan because the '800 patent specifically teaches the benefit of the inclusion of a protease inhibitor as an element of a pharmaceutical composition for the treatment of IL-ip mediated disease states, including MS.

In response, applicants note that, as the Examiner has acknowledged, the '791 and '981 patents do not teach the use of protease inhibitors in a medicament for multiple sclerosis.

Nor do these references alone or in combination teach, suggest or motivate the use of microcrystalline cellulose in excess of 50%. Furthermore, since the '800 patent contains no disclosure teaching or suggestion combining a protease inhibitor with glatiramer acetate and microcrystalline cellulose in excess of 50%, applicants maintain that the invention claimed in claims 1 and 61 is novel and not obvious to one skilled in the art. Therefore, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1 and 61 based on obvious-type double patenting over the '791 and '981 patents in view of the '800 patent.

Double Patenting Over the '791 Patent in View of the '981 Patent and the '666 Patent

In section 6 of the March 24, 2004 final Office Action, the Examiner maintained the rejection of claims 43, 65 and 66 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 7-11 of the '791 patent in view of the '981 patent and U.S. Patent No. 4,129,666 to Wizerkaniuk ("the '666 patent"), for the reasons of record in the July 31, 2003 Office Action.

In the March 24, 2003 final Office Action, the Examiner noted that the applicants argued that the additional citation of the '666 patent does not render the combination of glatiramer acetate (copolymer-1), greater than 50% MCC and the use of a rotating pan apparatus for the application of an enteric coating obvious. The Examiner's comments regarding the combination of the disclosures of the '791 patent and the '981 patent have been discussed, *supra*, in section 3. The Examiner also alleged that the use of a rotating pan apparatus for the application of an enteric coating to the claimed medicament would have been obvious to the artisan because the use of such

an apparatus does not require the use of toxic solvents, thus being beneficial both for the recipient subject and for workers of the manufacturing facility.

In response, applicants note that, as the Examiner has acknowledged, the '791 and '981 patents do not recite the use of a rotating pan for application of the enteric coating to the solid form of the pharmaceutical composition. Nor do these references alone or in combination teach, suggest or motivate the use of microcrystalline cellulose in excess of 50%. Furthermore, the '666 patent contains no disclosure, teaching or suggestion combining the use of a rotating pan for application of the enteric coating to the solid form of the pharmaceutical composition with glatiramer acetate and microcrystalline cellulose in excess of 50%. None of these references individually or in combination teach or suggest treating multiple sclerosis with glatiramer acetate combined with microcrystalline cellulose in excess of 50% and with an enteric coating applied by the rotating pan method. Therefore, the applicants request that the Examiner reconsider and withdraw the obviousness-type double patenting rejection of claims 43, 65 and 66 over '791 patent in view of the '981 and '666 patents.

For all of the above reasons, applicants respectfully request that the Examiner withdraw the rejections under non-statutory obviousness-type double patenting.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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